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published in
Journal of Medicinal Chemistry
1999

DOI (link to publisher)
10.1021/jm9810912

document version
Publisher's PDF, also known as Version of record

Journal of
Medicinal
Chemistry

Volume 42, Number 7 April 8, 1999

Articles

Characterization of the Binding Site of the Histamine H_3 Receptor. 1. Various Approaches to the Synthesis of 2-(1*H*-Imidazol-4-yl)cyclopropylamine and Histaminergic Activity of (1*R*,2*R*)- and (1*S*,2*S*)-2-(1*H*-Imidazol-4-yl)-cyclopropylamine

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Received October 1, 1998

Various approaches to the synthesis of all four stereoisomers of 2-(1*H*-imidazol-4-yl)cyclopropylamine (cyclopropylhistamine) are described. The rapid and convenient synthesis and resolution of *trans*-cyclopropylhistamine is reported. The absolute configuration of its enantiomers was determined by single-crystal X-ray crystallographic analysis. The distinct *trans*-cyclopropylhistamine enantiomers were tested for their activity and affinity on the histamine H_3 receptor. (1*S*,2*S*)-Cyclopropylhistamine (VUF 5297) acts as an agonist both on the rat cortex ($pD_2 = 7.1$; $\alpha = 0.75$) and on guinea pig jejunum ($pD_2 = 6.6$; $\alpha = 0.75$). Its enantiomer, (1*R*,2*R*)-cyclopropylhistamine (VUF 5296), is about 1 order of magnitude less active. Both enantiomers show weak activity on H_1 and H_2 receptors. All synthetic attempts to *cis*-cyclopropylhistamine were unsuccessful. Nevertheless, the results of this study provide an ideal template for molecular modeling studies of histamine H_3 receptor ligands.

Introduction

Next to its role as mediator in (patho)physiological processes, histamine can be regarded as a neurotransmitter.[1] The different pharmacological actions of histamine[2] are mediated via the activation of distinct histamine receptor subtypes. In addition to two postsynaptic receptor subtypes, H_1 and H_2, a presynaptic H_3 receptor has been identified. The histamine H_3 receptor is responsible for controlling neuronal synthesis of histamine and in addition regulates the release of the neurotransmitter into the synaptical cleft.[3] Furthermore, the receptor has been shown to modulate the release of other neurotransmitters, e.g., serotonin,[4,5] acetylcholine,[6] dopamine,[7] and noradrenaline,[8] in both the central nervous system (CNS) and the peripheral nervous system. Therefore the H_3 receptor can be considered a potential target for the development of new therapeutic agents, e.g., to treat neurologic disorders.[9] To determine the precise functional roles of the H_3 receptor, it is necessary to develop potent and selective H_3 ligands. Design of such compounds can be facilitated by molecular modeling. Furthermore, such studies can help to better understand the molecular mechanisms involved in receptor stimulation. Therefore, the struc-

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10.1021/jm9810912 CCC: $18.00
Published on Web 03/12/1999

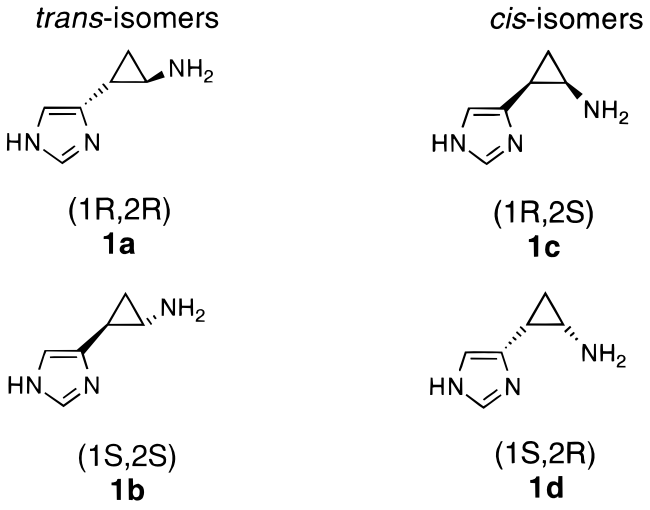


Figure 1. Stereoisomers of cyclopropylhistamine (**1**).

tural features that are responsible for affinity and intrinsic activity of a ligand need to be resolved.

The development of rigid histamine analogues will contribute to the determination of the H_3 receptor pharmacophore, as the conformations of these compounds only allow restricted spatial orientation of the pharmacophoric elements of H_3 receptor agonists, i.e., the orientation of the imidazole ring with respect to the basic nitrogen in the side chain of the ligands. A small and rigid compound such as 2-(1*H*-imidazol-4-yl)cyclopropylamine (cyclopropylhistamine) (**1**) would be an ideal template for the development of a pharmacophore model, using molecular modeling techniques. Some preliminary pharmacological data for this compound have been reported in a patent application by Arrang et al.[10] Unfortunately, the stereochemical identity of the material tested was not reported. Hence, we speculated that the results reported by Arrang and co-workers could be based on experiments with racemic mixtures of both the *trans*- and *cis*-diastereoisomers (denoted here as **1a**,**b** and **1c**,**d**, respectively; Figure 1). As the H_3 receptor has proved to be highly stereoselective,[11,12] it is reasonable to assume that each of the stereoisomers will have a different activity. For molecular modeling studies, the potencies of each of the distinct isomers has to be determined. Therefore, we decided to attempt to synthesize the four stereoisomers of cyclopropylhistamine and to study their respective H_3 pharmacology.

Chemistry

In the aforementioned patent application by Arrang et al.[10] cyclopropylhistamine (**1**) was obtained via a route developed by Burger and co-workers.[13] In this route, cyclopropylhistamine (**1**) was synthesized starting from urocanic acid (**2**), via the cyclopropanation of *sec*-butyl *trans*-3-(1-trityl-1*H*-imidazol-4-yl)acrylate (**(*E*)-3**) with dimethyloxosulfonium methylide followed by a Curtius rearrangement of the carboxylate group (Scheme 1). In our hands, the key step in this synthesis scheme, the cyclopropanation step, yielded a racemic mixture of *trans*-cyclopropane **4a**,**b** in a moderate yield (41%).

No cyclopropane product with the *cis*-configuration was detected in the reaction mixture. Efforts to obtain *cis*-cyclopropylhistamine (**1c**,**d**) via cyclopropanation of the isomeric *sec*-butyl *cis*-3-(1-trityl-1*H*-imidazol-4-yl)-acrylate[14] (**(*Z*)-3**) as starting material also failed. Only *trans*-cyclopropanane product **4a**,**b** was obtained. Variation of the reaction conditions and use of other protective groups for the imidazole moiety or the carboxylate group could neither improve the yield nor improve the stereochemical outcome of the reaction. The addition of sulfonium ylide to the double bond proceeds via a nonconcerted reaction mechanism, and theoretically the formation of a mixture of all four cyclopropane stereoisomers is possible. However, we have to conclude that the addition to urocanic acid derivatives exclusively leads to the thermodynamically most stable product having the *trans*-cyclopropane configuration, regardless of the configuration of the unsaturated bond in the starting material.

Subsequently, we investigated other methods to obtain this compound in a stereoselective manner. Cyclopropanation of the urocanate **(*E*)-5** by the stereospecific addition of diazomethane, using palladium(II) acetate as a catalyst, gave the *trans*-cyclopropane **6a**,**b** in a moderate yield (Scheme 2). However, it must be noted that higher temperatures, larger amounts of catalyst, and repeated applications of the reaction conditions were required compared to the reported cyclopropanations of analogous non-imidazole α,β-unsaturated carboxylic esters.[15−17] Alkaline hydrolysis of the ester **6a**,**b** and subsequent Curtius rearrangement yielded the racemic *trans*-cyclopropylhistamine (**1a**,**b**). Having obtained only a limited amount of *trans*-cyclopropylhistamine (**1a**,**b**) we were unable to separate the enantiomers.

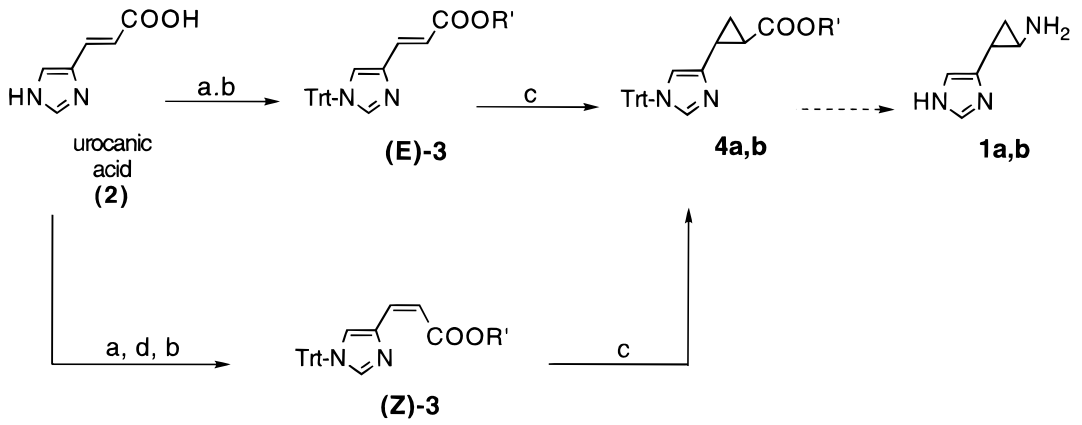
For the synthesis of the *cis*-isomers of cyclopropylhistamine (**1c**,**d**), the intermediate *cis*-urocanate **(*Z*)-5** was prepared by a new synthetic pathway (Scheme 3). 4-Iodo-1*H*-imidazole (**7**) protected with an *N*,*N*-dimethylsulfamoyl group was coupled to trimethylsilylacetylene in a palladium-catalyzed reaction.[17,18] Removal of the trimethylsilyl group by treatment with KOH gave the acetylenic derivative **10** which was treated with ethylmagnesium bromide and dimethyl carbonate to provide alkyne ester **11**. Subsequent hydrogenation over Lindlar catalyst[19] yielded the *cis*-urocanate **(*Z*)-5**. However, palladium-catalyzed cyclopropanation of this compound failed. All attempts to perform this reaction under the same, or even more drastic, conditions compared to the *trans*-urocanate **(*E*)-5** did not give the desired product; only starting material was recovered.

Other metal-catalyzed cyclopropanation procedures (e.g., Simmons−Smith reactions) on *trans*-urocanic acid derivatives such as **(*E*)-5** gave even lower yields of *trans*-cyclopropanated product. When using *cis*-urocanic acid derivatives such as **(*Z*)-5**, these methods failed completely to give cyclopropanated product. We suggest that the transition-metal-catalyzed cyclopropanations are seriously hampered because of chelation of the catalyst by the imidazole moiety.

We had to conclude that the strategy to synthesize all isomers of cyclopropylhistamine (**1**) by cyclopropanation of imidazole-containing precursors suffered from serious drawbacks. The *trans*-isomers **1a**,**b** were obtained in a moderate yield, and the limited availability of the racemic compound hampered efforts to separate the enantiomers. Furthermore, all attempts to synthesize the *cis*-isomers **1c**,**d** failed.

Therefore, we changed our strategy and developed a

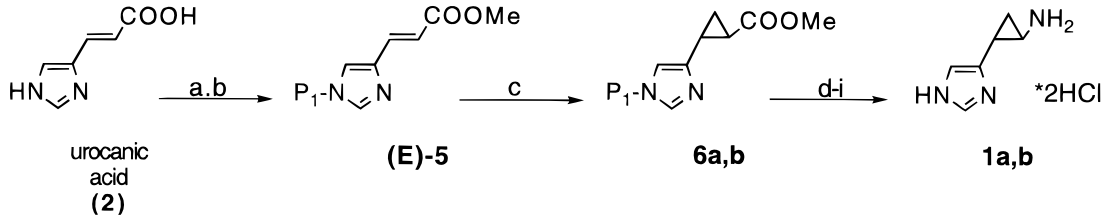
Scheme 1[a]



R'- = $CH_3CH_2CH(CH_3)$-

[a] Reagents used: (a) *sec*-butyl alcohol, H_2SO_4; (b) Trt-Cl, Et_3N, CH_2Cl_2; (c) $Me_3SO^-I^+$, NaH, DMF; (d) λ = 254 nm, CH_2Cl_2.

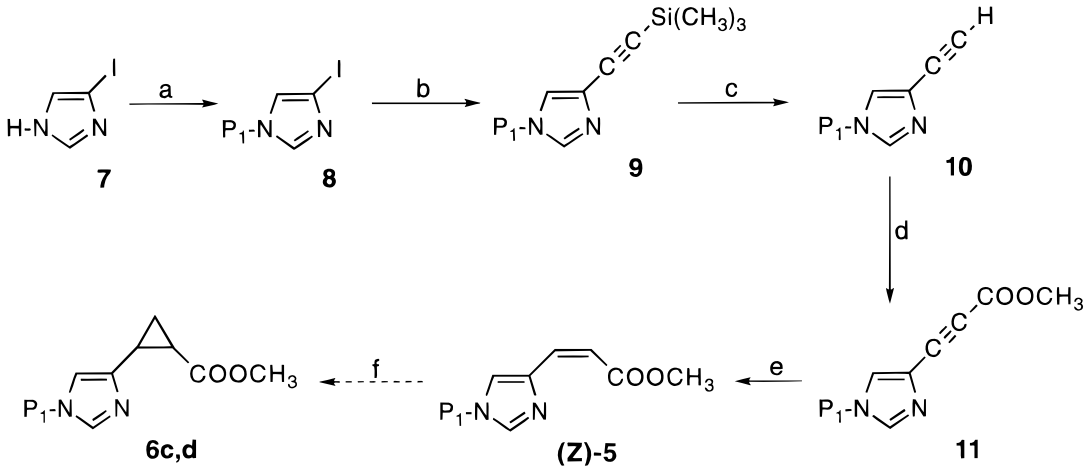
Scheme 2[a]



P_1- = Me_2NSO_2-

[a] Reagents used: (a) $HCl_{(g)}$, MeOH, reflux; (b) dimethylsulfamoyl chloride, Et_3N, DCM; (c) CH_2N_2, cat. $Pd(OAc)_2$, DCM; (d) 1 M KOH, MeOH, THF; (e) ClCOOEt, Et_3N, acetone; (f) NaN_3, H_2O; (g) toluene, reflux; (h) *tert*-butyl alcohol, reflux; (i) 1 M HCl, reflux.

Scheme 3[a]



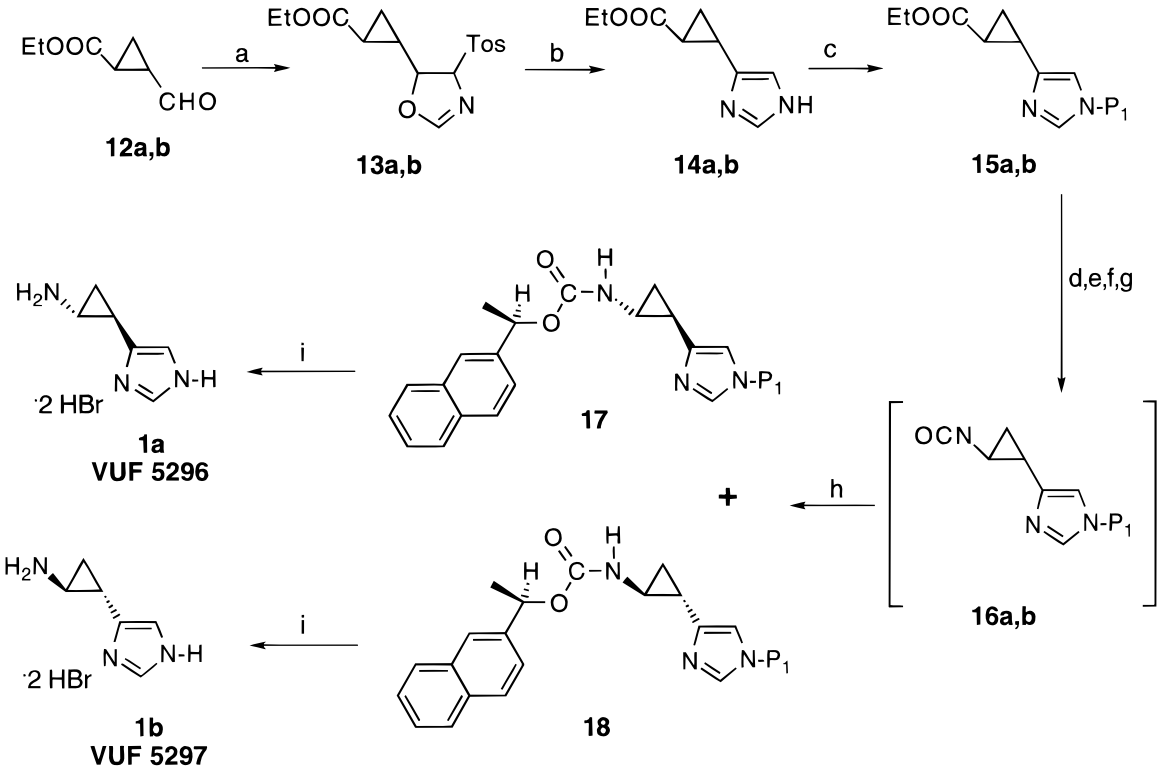
P_1- = Me_2NSO_2-

[a] Reagents used: (a) dimethylsulfamoyl chloride, Et_3N, toluene; (b) trimethylsilylacetylene, cat. $(C_6H_5)_3PdCl_2$, cat. CuI, Et_3N, 50 °C; (c) 2 M KOH, MeOH, THF; (d) EtMgBr, $(CH_3O)_2CO$; (e) H_2, Lindlar cat., quinoline, acetone; (f) CH_2N_2, cat. $Pd(OAc)_2$, DCM.

new synthesis route, constructing the imidazole ring on an appropriate cyclopropyl precursor (Scheme 4). Commercially available racemic ethyl *trans*-2-formyl-1-cyclopropanecarboxylate (**12a**,**b**) was allowed to react with (*p*-tolylsulfonyl)methyl isocyanide (TosMIC) in a [3+2] anionic cycloaddition.[20] The labile 4-tosyloxazoline **13a**,**b** which precipitated from the reaction mixture was filtered and immediately treated with a saturated solution of ammonia in ethanol at 120 °C. Both reaction steps proceed rapidly and in high yields.

The imidazole nucleus in **14a**,**b** was protected with a dimethylsulfamoyl group, and the ester **15a**,**b** was hydrolyzed under basic conditions. Subsequent Curtius rearrangement gave the isocyanate **16a**,**b** which was converted directly into the diastereomeric carbamates **17** and **18** using the enantiopure alcohol (*R*)-(+)-1-(2-naphthyl)ethanol. The diastereomers were easily separated by flash column chromatography. The diastereomeric purity of the isolated stereoisomers was verified by HPLC analysis. The absolute configuration of **18** was

Scheme 4[a]



P_1- = Me_2NSO_2-

[a] Reagents used: (a) tosmic, NaCN, EtOH, 0 °C; (b) EtOH/NH_3, 120 °C, 15 bar; (c) Me_2NSO_2-Cl, Et_3N, CH_2Cl_2; (d) KOH, THF, MeOH; (e) $ClCO_2C_2H_5$, Et_3N, acetone; (f) NaN_3, H_2O; (g) toluene, Δ; (h) (*R*)-(+)-1-(2-naphthyl)ethanol, toluene; (i) 30% HBr, Δ.

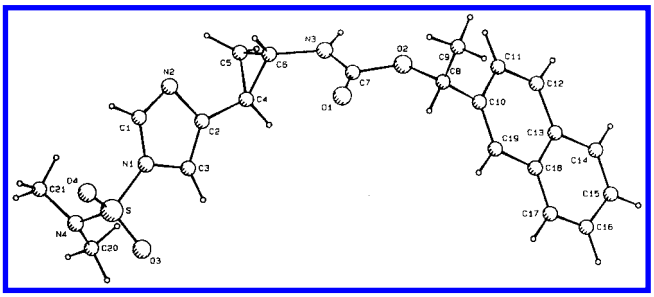


Figure 2. ORTEP drawing of **18**.

determined by single-crystal X-ray analysis (Figure 2) (for details, see the Experimental Section).

Hydrolysis of the distinct diastereoisomers with hydrobromic acid gave the enantiopure *trans*-cyclopropylhistamines (**1a**,**b**).

In an attempt to prepare *cis*-cyclopropylhistamine (**1c**,**d**) via an analogous route, racemic ethyl *cis*-2-formylcyclopropylcarboxylate[21] was reacted with TosMIC. This resulted in the precipitation of a highly unstable compound that could not be characterized. Immediate treatment of this material with ammonia in ethanol resulted in the formation of tars from which no cyclopropylimidazoles could be isolated or identified.

Pharmacological Data

The agonistic activities of the compounds **1a**,**b** on the histamine H_3 receptor were determined on an in vitro test system based on the electrically evoked contractile response of isolated guinea pig jejunum segments.[22] The receptor activities were also measured via the release of [^{3}H]noradrenaline from electrically stimulated rat cerebral cortex slices.[23] Binding affinities were determined using an H_3 receptor binding assay on rat cortex (for details, see the Experimental Section). The compounds were additionally tested for H_2 agonism on the spontaneously beating guinea pig right atrium[24] and for H_1 agonism on guinea pig ileum segments (Table 1).[25]

Table 1. Agonistic Activities, Intrinsic Activity (α), and Binding Affinity of the Enantiopure *trans*-Cyclopropylhistamines

		H_3			H_2	H_1
compound	configuration	pD_2[a]	pD_2[b]	pK_i[c]	pD_2[d]	pD_2[e]
histamine		7.4 ± 0.1 (α = 1.0)	7.4 ± 0.1 (α = 1.0)	8.2 ± 0.1	6.1 ± 0.1 (α = 1.0)	6.6 ± 0.1 (α = 1.0)
1a (VUF 5296)	1*R*,2*R*	5.75 ± 0.39 (α = 0.64)	6.15 ± 0.08 (α = 0.32)	7.60 ± 0.1	4.9 ± 0.1 (α = 0.9)	4.5 ± 0.1 (α = 0.9)
1b (VUF 5297)	1*S*,2*S*	7.08 ± 0.15 (α = 0.71)	6.64 ± 0.06 (α = 0.75)	8.76 ± 0.1	4.8 ± 0.1 (α = 1.0)	5.0 ± 0.1 (α = 1.2)

[a] Functional H_3 receptor assay on rat cortex. [b] Functional H_3 receptor assay on guinea pig jejunum. [c] H_3 receptor binding assay on rat cortex. [d] Functional H_2 receptor assay on guinea pig atrium. [e] Functional H_1 receptor assay on guinea pig jejunum.

Discussion

The histamine H_3 receptor affinity of cyclopropylhistamine (**1**) has been reported in a patent application by Arrang et al.[10] We assume that the material tested by Arrang and co-workers was a racemic mixture of *trans*-cyclopropylhistamine (**1a**,**b**). In our efforts to synthesize all four stereoisomers, we have developed a new route for the large-scale synthesis and resolution of *trans*-cyclopropylhistamine (**1a**,**b**). However, all synthetic attempts to *cis*-cyclopropylhistamine (**1c**,**d**) were unsuccessful.

Pharmacological evaluation of the enantiopure products **1a**,**b** confirmed once more the stereoselectivity of the H_3 receptor. We established (1*S*,2*S*)-2-(1*H*-imidazol-4-yl)cyclopropylamine (**1b**) (VUF 5297) as the eutomer, having moderate H_3 activity. Its enantiomer VUF 5296 is about 10 times less potent. Both stereoisomers show partial agonistic activity. Minor differences in potencies between the two functional assays were found. Therefore, the suggested H_3 receptor heterogeneity[2] is not manifested by compounds **1a**,**b**.

During the preparation of this manuscript, Khan et al.[26] reported the synthesis of *trans*-cyclopropylhistamine (**1a**,**b**) via a diastereomeric synthesis route analogous to the route developed by Burger et al.[13] Surprisingly, they reported (1*R*,2*R*)-2-(1*H*-imidazol-4-yl)cyclopropylamine (**1a**) to be the most active enantiomer. Unfortunately, no analytical characterization of the ligands was reported by Khan and co-workers; we were therefore unable to compare the optical rotation of the cyclopropylhistamines prepared in the different laboratories. It should be noted that a modeling study by Sippl et al.[27] suggested that (1*S*,2*S*)-cyclopropylhistamine (**1b**) provided the best sterical agreement with the derived H_3 receptor pharmacophore model. Our present study supports these theoretical findings.

The rigid cyclopropylhistamine derivatives show only a moderate to low H_1 and H_2 receptor activity. The histamine H_1 receptor has a slight preference for the (1*S*,2*S*)-enantiomer **1b**.

Conclusion

A rapid and convenient synthesis and resolution of *trans*-2-(1*H*-imidazol-4-yl)cyclopropylamine (*trans*-cyclopropylhistamine) is described. (1*S*,2*S*)-2-(1*H*-imidazol-4-yl)cyclopropylamine (VUF 5297) (**1b**) is a rigid H_3 receptor agonist about 10 times more active as its enantiomer. These results have enabled us to construct an unambiguous pharmacophore model for the histamine H_3 receptor, explaining agonistic and antagonistic activity of histamine H_3 ligands, as will be published elsewhere.[28]

Experimental Section

Chemistry. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer with tetramethylsilane as an internal standard. Mass spectra were recorded on a Finnigan MAT-90 spectrometer. Melting points were determined on a Mettler FP-5 + FP-52 apparatus and are uncorrected. GLC analysis was performed on a Shimadzu GC-14A instrument equipped with an FID detector and an HP1 column (50 m × 0.31 mm). Elemental analyses was performed by Micro Kemi AB, Uppsala, Sweden. Solvents were purified and dried by standard procedures before use.

Methyl (*E*)-3-(1*H*-Imidazol-4-yl)acrylate. Urocanic acid (25.0 g, 0.18 mol) was added to refluxing methanol (150 mL), and HCl gas was bubbled through the mixture, according to literature procedures.[29] After refluxing for 5 h, the clear solution was cooled to 5 °C and white needlelike crystals appeared (32.20 g, 94.4%). Mp: 233.5−234.5 °C.

Methyl (*E*)-3-(1-(*N*,*N*-Dimethylsulfamoyl)-1*H*-imidazol-4-yl)acrylate (5). Methyl (*E*)-3-(1*H*-imidazol-4-yl)acrylate (32.20 g, 0.17 mol) was dissolved in a solution of dichloromethane (600 mL) and triethylamine (75 mL). After the addition of *N*,*N*-dimethylsulfamoyl chloride (20.0 mL, 0.19 mol), the reaction mixture was refluxed for 48 h. The solution was washed with H_2O (150 mL) and saturated aqueous sodium chloride (150 mL). After evaporation of the dichloromethane, a white solid (43.37 g) remained. Recrystallization from 2-propanol resulted in white crystals (37.55 g, 84.8%). Mp: 137.0−138.0 °C. ^{1}H NMR ($CDCl_3$): δ 2.89 (s, 6H, NCH_3), 3.80 (s, 3H, OCH_3), 6.67 (d, J = 15.6 Hz, 1H), 7.38 (s, 1H), 7.52 (d, J = 15.6 Hz, 1H), 7.90 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 38.2, 51.7, 118.7, 119.1, 134.4, 137.5, 139.3, 167.3. Anal. ($C_9H_{13}N_3O_4S$) C, H, N.

***trans*-2-(1-(*N*,*N*-Dimethylsulfamoyl)-1*H*-imidazol-4-yl)-cyclopropanecarboxylic Acid.** A solution of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazogen) (40.0 g, 0.19 mol) dissolved in ether (200 mL) was added dropwise to a heated mixture of KOH (31.0 g, 0.55 mol in 200 mL of H_2O) and 2-(2-ethoxyethoxy)ethanol (200 mL); special 'soft' glassware was used. The hence generated etheric diazomethane solution was distilled dropwise into a solution of (*E*)-**5** (5.0 g, 19.3 mmol) and $Pd(OAc)_2$ (200 mg) in dichloromethane (1 L) at room temperature. The light-yellow solution became dark-brown, and N_2 evolution was observed. The reaction mixture was stirred overnight. After the addition of a few drops acetic acid, the reaction mixture was washed with 5% $NaHCO_3$ solution (250 mL). The organic layer was dried over Na_2SO_4, filtered over a short silica column, and concentrated in vacuo. The remaining light-yellow oil consisted of 49% product **6a**,**b** and 51% starting material (GC and ^{1}H NMR). The residue was dissolved in dichloromethane (1 L), and the procedure was repeated, employing the same amounts of reagents. This time the residual oil consisted of 82% cyclopropane product and 18% starting material. ^{1}H NMR ($CDCl_3$) **6a**,**b**: δ 1.42−1.57 (m, 2H), 2.03−2.13 (m, 1H), 2.30−2.48 (m, 1H), 2.84 (s, 6H), 3.70 (s, 3H), 7.08 (s, 1H), 7.77 (s, 1H).

The crude product was dissolved in a mixture of methanol (100 mL) and tetrahydrofuran (100 mL). A portion of 1 M KOH solution (100 mL) was added, and after 0.5 h of stirring at room temperature, the mixture was washed with dichloromethane (3 × 200 mL). The aqueous layer was treated with 1 M HCl solution until the mixture had a pH of 2. The product was extracted with dichloromethane (3 × 200 mL), and after drying over Na_2SO_4, filtration, and evaporation of the dichloromethane, a light-brown solid (3.91 g) remained. After several triturations with dry acetone, a white powder (2.92 g, 58.4%) was collected. Mp: 166.0 °C. ^{1}H NMR (DMSO-d_6): δ 1.28−1.37 (m, 2H), 1.78−1.88 (m, 1H), 2.28−2.38 (m, 1H), 2.78 (s, 6H), 7.50 (s, 1H), 8.00 (s, 1H), 12.28 (bs, 1H). ^{13}C NMR (DMSO-d_6): δ 14.8, 18.7, 22.0, 37.7, 114.1, 136.7, 141.5, 173.8. Anal. ($C_9H_{13}N_3O_4S$) C, H, N.

***trans*-2-(1*H*-Imidazol-4-yl)cyclopropylamine (1a,b).** Racemic *trans*-2-(1-(*N*,*N*-dimethylsulfamoyl)-1*H*-imidazol-4-yl)-cyclopropanecarboxylic acid (2.22 g, 8.6 mmol) was dissolved in dry acetone (65 mL) and triethylamine (1.6 mL, 11.5 mmol) under N_2 atmosphere. The reaction mixture was cooled to 0 °C, and ethyl chloroformate (1.6 mL, 16.7 mmol) was added dropwise (a white precipitate formed). After 2 h, a solution of sodium azide (0.85 g, 13.1 mmol in 15 mL of H_2O) was added slowly, and the mixture was stirred for another hour. After addition of H_2O (65 mL), the solution was concentrated in vacuo until the water layer remained. The water layer was extracted with toluene (3 × 65 mL), and the combined toluene layers were dried over Na_2SO_4, filtered, and refluxed for 2 h (N_2 evolution was observed). The residue after evaporation of toluene was refluxed in *tert*-butyl alcohol (50 mL) for 12 h

(disappearance of the isocyanate peak in IR spectrum). After evaporation of the alcohol a dark residue remained. This residue was dissolved in ethyl acetate and filtered over a short silica column. A white solid (2.10 g) remained after evaporation of the ethyl acetate. This was refluxed for 12 h in 1 M HCl (100 mL). After concentration in vacuo, the residue was refluxed in absolute ethanol (60 mL) for 0.5 h, concentrated, and subsequently washed with acetone. A beige solid (1.06 g, 63%) remained, which was recrystallized from 2-propanol/ether. Mp: 187.0−187.5 °C. ^{1}H NMR (D_2O): δ 1.42 (ddd, J = 6.7, 6.9 and 8.2 Hz, 1H), 1.55 (ddd, J = 4.7, 7.2 and 10.2 Hz, 1H), 2.51 (ddd, J = 3.4, 6.5 and 10.1 Hz, 1H), 3.03 (ddd, J = 3.6, 4.5 and 8.2 Hz, 1H), 7.25 (s, 1H), 8.57 (s, 1H). ^{13}C NMR (D_2O): δ 12.4, 12.5, 30.7, 117.4, 132.4, 134.9. Anal. ($C_6H_9N_3$·2HCl) C, H, N.

1-(*N*,*N*-Dimethylsulfamoyl)-4-iodo-1*H*-imidazole (8). *N*,*N*-Dimethylsulfamoyl chloride (12.0 mL, 0.11 mol) was added to a solution of 4-iodo-1*H*-imidazole (**7**) (20.0 g, 0.10 mol) in dichloromethane (600 mL) and triethylamine (40 mL). The reaction mixture was refluxed for 60 h and subsequently washed with H_2O (250 mL) and 5% $Na_2S_2O_3$ solution (250 mL). A light-brown solid (30.22 g) remained after evaporation of the solvents. Recrystallization from hot 2-propanol resulted in white crystals (8.65 g, 60%). Mp: 131.5 °C. ^{1}H NMR ($CDCl_3$): δ 2.89 (s, 6H), 7.34 (s, 1H), 7.78 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 38.2, 84.4, 122.7, 137.8. Anal. ($C_5H_8N_3O_2SI$) C, H, N.

Methyl (1-(*N*,*N*-Dimethylsulfamoyl)-1*H*-imidazol-4-yl)-propynoate (11). To a solution of **8** (20.0 g, 67 mmol) in triethylamine (250 mL) was added bis(triphenylphosphine)-paladium(II) chloride (1 mol %, 0.5 g), CuI (1 mol %, 130 mg), and trimethylsilylacetylene (20.0 mL, 141 mmol). This reaction mixture was stirred for 60 h on a 50 °C oil bath. After filtration of the reaction mixture, the solution was concentrated in vacuo. ^{1}H NMR ($CDCl_3$) **9**: δ 0.25 (s, 9H), 2.87 (s, 6H), 7.40 (s, 1H), 7.81 (s, 1H).

The residue **9** was dissolved in methanol (150 mL) and tetrahydrofuran (150 mL). A solution of 2 M potassium hydroxide (150 mL) was added, and the mixture was poured in a saturated NH_4Cl solution (150 mL). After extraction of the product with dichloromethane (1 × 300 mL, 2 × 100 mL), drying over Na_2SO_4, filtration, and evaporation of the solvent, a brown oil (12.3 g) remained. The oil was purified by column chromatography using ethyl acetate as eluent (R_f = 0.7). A light-beige solid (1-(*N*,*N*-dimethylsulfamoyl)-4-ethynyl-1*H*-imidazole) (7.82 g, 59%) was isolated. ^{1}H NMR ($CDCl_3$) **10**: δ 2.88 (s, 6H), 3.13 (s, 3H), 7.42 (s, 1H), 7.83 (s, 1H).

This beige solid **10** (5.0 g, 25 mmol) was dissolved in dichloromethane (50 mL) and added dropwise to a Grignard mixture, prepared from magnesium (0.8 g, 33 mmol) and ethyl bromide (2.5 mL, 33 mmol) in tetrahydrofuran (5 mL). After 1 h the mixture was poured in dimethyl carbonate (100 mL) and stirred overnight. The solution was poured in H_2O (250 mL) and extracted with dichloromethane (3 × 200 mL). After evaporation of the solvents, a brown oil (5.53 g) remained, which was purified on a silica gel column with ethyl acetate as eluent (R_f = 0.8). After two recrystallizations from 2-propanol, white crystals (2.98 g, 46%) were collected. Mp: 126.0−127.0 °C. ^{1}H NMR ($CDCl_3$) **11**: δ 2.91 (s, 6H, NCH_3). 3.84 (s, 3H), 7.63 (s, 1H), 7.88 (s, 1H). ^{13}C NMR ($CDCl_3$) **11**: δ 38.2, 52.9, 78.6, 82.1, 123.2, 124.6, 137.1, 154.0. Anal. ($C_9H_{11}N_3O_4S$) C, H, N.

Methyl (*Z*)-3-(1-(*N*,*N*-Dimethylsulfamoyl)-1*H*-imidazol-4-yl)acrylate (5). Compound **11** (2.6 g, 10.1 mmol) was dissolved in acetone (75 mL). Lindlar catalyst (120 mg) and quinoline (300 mg) were added, and the reaction mixture was stirred under hydrogen atmosphere (1 atm). After hydrogen consumption had ceased, additional Lindlar catalyst was added (repeated twice; a total of 280 mg of catalyst extra was added). After 8 h and 300 mL of hydrogen gas consumption, the reaction mixture was filtered and concentrated in vacuo. The residue consisted of 92% *cis*- and 8% *trans*-isomer, according to GC. This was purified on a silica gel column with ethyl acetate as eluent (R_f = 0.5) and recrystallization from *n*-hexane. White crystals (1.8 g, 69%) were isolated. Mp: 74.0 °C. ^{1}H NMR ($CDCl_3$): δ 2.92 (s, 6H), 3.76 (s, 3H), 5.95 (d, J = 12.7 Hz, 1H), 6.96 (d, J = 12.2 Hz, 1H), 7.88 (s, 1H), 8.64 (s, 1H). Anal. ($C_9H_{13}N_3O_4S$) C, H, N.

Ethyl *trans*-2-(4-(Methylphenyl)sulfonyl-4,5-dihydrooxazol-5-yl)cyclopropanecarboxylate (13a,b). To a stirred suspension of tosylmethyl isocyanide (6.8 g, 34.6 mmol) and ethyl *trans*-2-formyl-1-cyclopropanecarboxylate (**12a**,**b**) (5.0 g, 35.2 mmol) in absolute ethanol (250 mL) at 0 °C was added sodium cyanide (45 mg). For a moment the reaction mixture became clear followed by precipitation of the product. Ten minutes after the addition of sodium cyanide, the suspension was filtered and product was washed with ether/hexane (20 mL, 1/1, v/v) and dried in vacuo. The product was isolated as a white hygroscopic solid (9.9 g, 85%). Mp: 107.0 °C. ^{1}H NMR ($CDCl_3$): δ 0.96−1.06 (m, 1H), 1.25 (t, J = 7.14 Hz, 3H), 1.55−1.77 (m, 2H), 1.79−1.89 (m, 1H), 2.55 (s, 3H), 4.12 (q, J = 7.14 Hz, 2H), 4.72 (dd, 1H, J = 4.11, 4.11 Hz), 4.92 (dd, J = 4.11, 1.63 Hz, 1H), 6.97 (d, J = 1.63 Hz, 1H), 7.36 (d, J = 8.16 Hz, 2H), 7.80 (d, J = 8.16 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 12.39, 14.00, 16,77, 21.55, 24.20, 60.84,79.32, 89.72, 129.07, 129.72, 132.69, 145.56, 159.16, 172.37.

Ethyl *trans*-2-(1*H*-Imidazol-4-yl)cyclopropanecarboxylate (14a,b). In a stainless steal bomb, a solution of oxazoline **13a**,**b** (9.0 g, 26.7 mmol) and saturated solution of ammonia in absolute ethanol (120 mL) was heated at 120 °C for 25 h. The pressure increased to 12 atm. After cooling, the solvent was removed under reduced pressure. The dark, oily residue was dissolved in ethyl acetate/dichloromethane (150 mL, 4/1, v/v) and washed with saturated aqueous sodium chloride (5 × 50 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo to give the product as an oil (3.56 g, 74%). ^{1}H NMR ($CDCl_3$): δ 1.18 (t, J = 7.14 Hz, 3H), 1.28−1.38 (m, 1H), 1.39−1.48 (m, 1H), 1.82−1.93 (m, 1H), 2.37−2.48 (m, 1H), 4.06 (q, J = 7.14 Hz, 2H), 6.77 (s, 1H), 7.45 (s, 1H).

Ethyl *trans*-2-(1-(*N*,*N*-Dimethylsulfamoyl)-1*H*-imidazol-4-yl)cyclopropanecarboxylate (15a,b). To a solution of **14a**,**b** (3.00 g, 16.9 mmol) and triethylamine (5.0 mL, 36.1 mmol) in dichloromethane (70 mL) was added *N*,*N*-dimethylsulfamoyl chloride (3.1 mL, 28.9 mmol). Subsequently, the reaction mixture was refluxed for 22 h. Concentration under reduced pressure followed by flash column chromatography (ethyl acetate/hexane, 5/3, v/v, R_f = 0.5) gave the product as a yellow oil (4.13 g, 85%). ^{1}H NMR ($CDCl_3$): δ 1.26 (t, J = 6.67 Hz, 3H), 1.37−1.58 (m, 2H), 1.98−2.10 (m, 1H), 2.36−2.48 (m, 1H), 2.87 (s, 6H), 4.14 (q, J = 6.67 Hz, 2H), 7.04 (s, 1H), 7.72 (s, 1H).

***trans*-2-(1-(*N*,*N*-Dimethylsulfamoyl)-1*H*-imidazol-4-yl)-cyclopropanecarboxylic Acid.** Compound **15a**,**b** (2.5 g, 8.69 mmol) was dissolved in a mixture of methanol (100 mL) and THF (100 mL). At room temperature, 1 M KOH solution (100 mL) was added, and after 0.5 h stirring, the mixture was washed with dichloromethane (3 × 100 mL). The water layer was acidified with 1 M HCl until a pH of 2 and extracted with dichloromethane (3 × 100 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo to give a white powder (2.25 g, 75%). Mp: 166.0 °C. ^{1}H NMR (DMSO-d_6): δ 1.28−137 (m, 2H), 1.78−1.88 (m, 1H), 2.28−2.38 (m, 1H), 2.78 (s, 6H), 7.50 (s, 1H), 8.00 (s, 1H), 12.28 (bs, 1H). Anal. ($C_9H_{13}N_3O_4S$) C, H, N.

1′(*R*)-1-(2-Naphthyl)ethyl *trans*-[2-(1-(*N*,*N*-Dimethylsulfamoyl)-1*H*-imidazol-4-yl)cyclopropyl]carbamate (17, 18). To a solution of racemic *trans*-2-(1-(*N*,*N*-dimethylsulfamoyl)-1*H*-imidazol-4-yl)cyclopropanecarboxylic acid (4.44 g, 17.2 mmol) and triethylamine (3.2 mL, 3.0 mmol) in acetone (125 mL) at 0 °C was added dropwise ethyl chloroformate (3.2 mL, 33.4 mmol). After 2 h, a solution of sodium azide (1.70 g, 26.2 mmol) in H_2O (25 mL) was added slowly to the formed suspension and stirred for an additional hour. After addition of water (100 mL), the solution was extracted with toluene (3 × 100 mL). The organic layer was dried over sodium sulfate. After filtration, the solution was refluxed for 2 h (N_2 evolution was observed). Subsequently, (*R*)-(+)-1-(2-naphthyl)ethanol (3.26 g, 18.9 mmol) was added. The mixture was refluxed for

13 h. After evaporation of the solvent, the diastereomeric carbamates were isolated using a short silica gel column (ethyl acetate, $R_f = 0.6$) to give a white powder (6.41 g, 87%). The ratio of diastereoisomers was determined using HPLC analysis as 50:50 (Chrompack CPtm SpherSi, eluent ethyl acetate/hexane, 60/40, v/v, at 1 mL/min; $P = 20$ bar) (**11** has a retention time of 19.68 min, and **12** has a retention time of 23.58 min). Subsequent separation by flash column chromatography (ethyl acetate/hexane, 4/1, v/v, $R_f = 0.26$) gave the separate diastereoisomers. The diastereomeric purity of the isolated compounds were verified by HPLC.

1′(*R*)-1-(2-Naphthyl)ethyl (1*R*,2*R*)-[2-(1-(*N*,*N*-Dimethylsulfamoyl)-1*H*-imidazol-4-yl)cyclopropyl]carbamate (17). $R_f = 0.60$ (ethyl acetate). Mp: 156.0−157.0 °C. $[\alpha]^{30}_{546} = +65.0°$ (*c* 0.24, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.04−1.19 (m, 1H), 1.23−1.33 (m, 1H), 1.56 (d, $J = 6.58$ Hz, 3H), 1.91−2.01 (m, 1H), 2.70 (s, 6H), 2.82−2.98 (m, 1H), 5.53 (bs, 1H), 5.94 (q, $J = 6.58$ Hz, 1H), 6.97 (s, 1H), 7.44−7.46 (m, 3H), 7.72−7.80 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.68, 18.10, 22.27, 31.74, 37.89, 72.77, 112.99, 123.92, 124.66, 125.83, 126.03, 127.48, 127.85, 128.13, 132.78, 132.99, 136.05, 139.28, 142.89, 156.31.

(1′*R*)-1-(2-Naphthyl)ethyl (1*S*,2*S*)-[2-(1-(*N*,*N*-Dimethylsulfamoyl)-1*H*-imidazol-4-yl)cyclopropyl]carbamate (18). $R_f = 0.57$ (ethyl acetate). Mp: 157.0−158.5 °C. $[\alpha]^{30}_{546} = +5.6°$ (*c* 0.24, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.04−1.19 (m, 1H), 1.23−1.33 (m, 1H), 1.58 (d, $J = 6.58$ Hz, 3H), 1.91−2.01 (m, 1H), 2.75 (s, 6H), 2.82−2.98 (m, 1H), 5,30 (bs, 1H), 5.95 (q, $J = 6.58$ Hz, 1H), 6.99 (s, 1H), 7.44−7.46 (m, 3H), 7.72−7.80 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.66, 18.10, 22.40, 31.19, 37.95, 72.88, 76.31, 76.94, 77.58, 112.98, 123.89, 124.65, 125.84, 126.03, 127.48, 127.86, 128.12, 132.78, 133.00, 136.05, 139.22, 142.88, 156.24. Single crystals of this diastereoisomer **18** were obtained by recrystallization from ethanol.

X-ray crystal data for 18: $C_{21}H_{24}N_4O_4S$, $M_r = 428.5$, monoclinic, $P2_1$, $a = 13.930(1)$ Å, $b = 5.4967(4)$ Å, $c = 15.928(1)$ Å, $V = 1138.7(1)$ Å^3, $Z = 2$, $D_x = 1.25$ g cm^{-3}, λ(Cu Kα) = 1.5418 Å, λ(Cu Kα) = 15.01 cm^{-1}, $F(000) = 452$, room temperature; final $R = 0.096$ for 876 observed reflections.

A crystal with approximate dimensions of 0.03 × 0.05 × 0.60 mm was used for data collection on an Enraf-Nonius CAD-4 diffractometer with graphite-monochromated Cu Kα radiation and $\omega-2\theta$ scan. A total of 2403 unique reflections were measured within the range $-16 \le h \le 15$, $0 \le k < 6$, $0 \le l \le 19$. Of these, 876 were above the significance level of $2.5\sigma(I)$. The range of $(\sin\theta)/\lambda$ was 0.034−0.609 Å^{-1} ($3.0 < \theta < 69.9°$). Two reference reflections (203, 212) were measured hourly and showed no decrease during the 57-h collecting time. In addition, 611 "Friedel" reflections were measured, which were used in the determination of the absolute configuration. Unit-cell parameters were refined by least-squares fitting procedure using 23 reflections with $68 < 2\theta < 78°$. Corrections for Lorentz and polarization effects were applied. The structure was solved by the PATTY option of the DIRDIF94 program system.[30] The hydrogen atoms restraining the latter in such way that the distance to their carrier remained constant at approximately 1.0 Å and keeping their displacement factors fixed at $U = 0.1$ Å, converged to $R = 0.096$, $R_w = 0.123$, $(\Delta/\sigma)_{max} = 0.09$, $S = 1.07$. A weighting scheme, $w = [10.0 + 0.01*(\sigma(F_{obs}))^2 + 0.0001/(\sigma(F_{obs}))]^{-1}$, was used. The secondary isotropic extinction coefficient[31,32] refined to $Ext = 0.08(3)$. The absolute structure parameter[33] refined to $X_{abs} = -0.04(20)$, thus confirming the correct enantiomer. A final difference Fourier map revealed a residual electron density between −0.7 and 1.3 e Å^{-3} in the vicinity of the S atom. Scattering factors were taken from Cromer and Mann[34] *International Tables for X-ray Crystallography* (1974). The anomalous scattering of S was taken into account. All calculations were performed with XTAL3.4,[35] unless stated otherwise.

(1*R*,2*R*)-2-(1*H*-Imidazol-4-yl)cyclopropylamine (VUF 5296) (1a). A solution of **17** (1.25 g, 2.92 mmol) in 30% HBr (75 mL) was refluxed for 22 h. After concentration in vacuo, the residue was refluxed in absolute ethanol for 0.5 h and subsequently washed with acetone. White crystals (0.64 g, 77%) were collected. Mp: 207.0−208.0 °C. $[\alpha]^{30}_{546} = +54.4°$ (*c* 0.35, H_2O). ^{1}H NMR (D_2O): δ 1.42 (ddd, $J = 6.7$, 6.9, and 8.2 Hz, 1H), 1.55 (ddd, $J = 4.7$, 7.2, and 10.2 Hz, 1H), 2.51 (ddd, $J = 3.4$, 6.5, and 10.1 Hz, 1H), 3.03 (ddd, $J = 3.6$, 4.5, and 8.2 Hz, 1H), 7.25 (s, 1H), 8.57 (s, 1H). Anal. ($C_6H_{11}N_3Br_2$) C, H, N.

(1*S*,2*S*)-2-(1*H*-Imidazol-4-yl)cyclopropylamine (VUF 5296) (1b). A solution of **18** (1.00 g, 2.33 mmol) in 30% HBr (75 mL) was refluxed for 22 h. After concentration in vacuo, the residue was refluxed in absolute ethanol for 0.5 h and subsequently washed with acetone. White crystals (0.51 g, 76%) were collected. Mp: 207.0−208.0 °C. $[\alpha]^{30}_{546} = -54.2°$ (*c* 0.35, H_2O). ^{1}H NMR (D_2O): δ 1.42 (ddd, $J = 6.7$, 6.9, and 8.2 Hz, 1H), 1.55 (ddd, $J = 4.7$, 7.2, and 10.2 Hz, 1H), 2.51 (ddd, $J = 3.4$, 6.5, and 10.1 Hz, 1H), 3.03 (ddd, $J = 3.6$, 4.5, and 8.2 Hz, 1H), 7.25 (s, 1H), 8.57 (s, 1H). Anal. ($C_6H_{11}N_3Br_2$) C, H, N.

Pharmacology. The compounds were tested for their activity on the histamine receptors in different assays (vide supra). These assays were previously described in detail.[22−25]

The histamine H_3 receptor affinity was determined in rat cortical membranes with [^{3}H]-N^α-methylhistamine (81.9 Ci/mmol; NEN Life Science Products, Brussels, Belgium) according to the method of West et al.[36] with modifications. Briefly animals were killed by decapitation, and the cerebral cortex was rapidly removed. Rat cortices were homogenized in 15 volumes (wt/vol) of ice-cold Tris/HCl buffer (50 mM Tris/HCl, 5 mM $MgCl_2$, 145 mM NaCl, pH 7.4 at 4 °C) using an Ultra-Turrax homogenizer (8 s) and a glass−Teflon homogenizer (four strokes up and down) subsequently. All subsequent steps were carried out at 0−4 °C. The homogenate was centrifuged at 800*g* for 10 min. The pellets were discarded, and the supernatant was centrifuged for 20 min at 40000*g*. The resulting pellet was resuspended, and the last centrifugation step was repeated. The pellet was resuspended in 1.5 volumes (wt/vol) of Tris/HCl buffer to give a final concentration of ∼300 μg/100 μL and stored in aliquots at −80 °C. Protein concentration was determined using Biorad protein assay (Bio-Rad Laboratories GmbH, Munich, Germany). Competition binding experiments were carried out in polypropylene tubes in a total volume of 400 μL of 50 mM Na^+ phosphate buffer, pH 7.4 at 37 °C, containing 30 μg of protein, 1 nM [^{3}H]-N^α-methylhistamine, and 0.1−10 000 nM compound to be tested. Samples were incubated for 40 min at 25 °C. The incubation was started by the addition of 100 μL of membranes (30 μg) and terminated by rapid filtration through poly(ethylenimine) (0.3 wt %/vol) pretreated Whatman GF/C filters using a Brandel filtration apparatus. The filters were washed twice with 3 mL of ice-cold Tris/HCl buffer (50 mM Tris/HCl, 5 mM $MgCl_2$, 145 mM NaCl, pH 7.4 at 4 °C). The radioactivity retained on the filters was measured using liquid scintillation counting. Competition isotherms were analyzed with the GraphPad Prism software (GraphPad, Intuitive Software for Science, San Diego, CA). K_i values were determined with the equation $K_i = IC_{50}/(1 + ([\text{ligand}]/K_d))$.

Acknowledgment. This research was in part (I. De Esch) supported by the Dutch Technology Foundation (STW). We would like to thank Dr. B. Windhorst for the HPLC analysis of the diastereomeric carbamates.

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JM9810912